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R^3 is Dpr, 4PyrAla or (L) or (D)Arg;

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R^4 is HomArg, Orn or Lys;

R^5 is (D)Gln or (L) or (D)Trp;

R^6 is (L) or (D)Gln or (p-NO_2)Phe; and

Y^2 is amide, thioether, thioester or disulfide.

REMARKS

Claims 12-28 have been cancelled and new claims 29-39 have been added. New claim 29 is directed to the backbone cyclized analog of claim 1 having a generic formula that encompasses formulas 3 and 4. Claim 37 is dependent on claim 32, being directed to a pharmaceutical composition wherein the IL-6 antagonist is a backbone cyclized peptide analog having a generic formula that encompasses formulas 3 and 4. The subject matter of original claims 12 and 13 is now encompassed in new claims 30 and 31 respectively.

Furthermore, original claims 14, 15, 16, 17, 18, 19 and 20 are represented by new claims 32, 33, 34, 35, 36, 38 and 39 respectively. The new claims are fully supported by the specification and original claims. No new matter has been added.

The inventorship for the present application is unchanged by these amendments.

Applicants elect the product claims 1-20. The Examiner has stated that claims 1-6 will be examined together with one of the following product groups I-III:

I. Claims 7-11, 15-18, drawn to peptides of formula 1 having a cyclized moiety and their compositions, classified in class 530, subclass 317;

II. Claims 12, 19, drawn to peptides of formula 3 having a cyclized moiety and their compositions, classified in class 530, subclass 317;

III. Claims 13, 20, drawn to peptides of formula 4 having a cyclized moiety and their compositions, classified in class 530, subclass 317.

In response to this restriction requirement, Applicants respectfully elect, with traverse, group II, directed to a backbone-cyclized peptide analog having IL-6 antagonist activity of claim 1 having the general structure of formula 3.

Applicants respectfully provide an example of a specific peptide covered by the elected formula to assist the Examiner in his search. Applicants direct the Examiner to page 27, table 1, fourth peptide in the table, 70003-20, as an elected peptide covered by the elected formula.

Claims 1-6, 29-32, and 37-39 are all readable upon the elected species.

Applicant reserves the right to pursue the subject matter of the cancelled claims in future applications. No fee is believed to be due for this submission. Should any fees be due, however, please charge such fees to Winston & Strawn Deposit Account No. 501-814.

Please direct all future correspondence to customer number 28765.

Respectfully submitted,

Date: 11/16/01

Allan A. Fanucci (Reg. No. 30,256)

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APPENDIX A

Please amend the specification as follows:

Please insert the paragraph on page 11, line 31, before "A more preferred" insert "**SEQ IDs NO: 1 to NO 32**, represent the embodiment of Formula No. 1 when each residue "R" is replaced by its potential amino acid in the L or D configuration. Only one sequence is representing both forms."

Please replace the paragraph on page 12, line 18, starting with "The currently most preferred backbone cyclized IL-6 antagonists of the invention which are derived from the IL-6 receptor molecule are as follows:
Trp-Arg-Lys-(D)Arg-Phe-AlaC3-Leu-Arg-(D)Tyr-AlaN3-NH_2 designated herein as PTR-5045 **(SEQ ID NO:25)**;
(D)Lys-Arg-(D)Leu-(D)Arg-(D)Phe-AlaC3-(D)Leu-Arg-(D)Tyr-AlaN3-NH_2 designated herein as PTR-5041 **(SEQ ID NO:18)**;
(D)Phe-Arg-(D)Leu-(D)Arg-(D)Phe-AlaC3-Leu-(D)Tyr-AlaN3-NH_2 designated herein as PTR-5043 **(SEQ ID NO:4)**."

Please replace the title on page 37, line 33, starting with "Example 1. Detailed synthesis of PTR 5045 **(SEQ ID NO:25)**"

Please replace the paragraph on page 39, line 7, starting with "Peptides were added to B16.F10.9 melanoma cells in the presence of 200 ng/ml IL-6 and 125 ng/ml sIL-6R. Incubation for three days. (Peptide concentration was calculated for average molecular weight of 1500 Da. Sequence of control peptides: PTR 5049 **(L Form of SEQ ID NO:25)**: Trp-Arg-Lys-(D)Arg-Phe-AlaC3-Leu-Arg-Tyr-AlaN3-NH_2. The results described in figure 2 show that PTR 5045 **(SEQ ID NO:25)** and PRT 5041 **(SEQ ID NO:18)** fully block IL-6 activity at concentration of about 250 nM while PTR 5049 **(L Form of SEQ ID NO:25)** and PTR 4041 **(SEQ ID NO:33)** are not active."

Please replace the paragraph on page 40, line 31, starting with "PTR 5045 **(SEQ ID NO:75)** was tested in this model in compare to the non-relevant control peptide PTR 4041

(SEQ ID NO:33) (Lys-GlyC2-Leu-Ile-Gln-Leu-Phe-GlyN3-Lys-Lys-NH_2). The results are summarized in the following table 3:"

Please replace the title on page 45, line 1, starting with "Table 4: Summary of synthesis and bioactivity of certain preferred PTRs (SEQ IDs NO:34 to NO:45)."

Please replace the title on page 46, line 1, starting with "Table 5: Certain preferred backbone cyclic peptide analogs capable of inhibiting IL-6 derived from either IL-6, IL-6R (SEQ IDs NO:46 to NO:76) or gp130."

Please replace the title on page 47, line 1, starting with "Table 6: Summary of activity of certain preferred analogs derived from the IL-6R (SEQ IDs NO:77 to NO:82)."

APPENDIX B

THE PRESENTLY PENDING CLAIMS

What is claimed is:

1. A backbone cyclized peptide analog having IL-6 antagonist activity, comprising a peptide sequence of five to twenty amino acids that incorporates at least one building unit, said building unit containing one nitrogen atom of the peptide backbone connected to a bridging group comprising an amide, thioether, thioester or disulfide, wherein the at least one building unit is connected via the bridging group to form a cyclic structure.

2. The backbone cyclized analog of claim 1 wherein the peptide sequence comprises six to twelve amino acids.

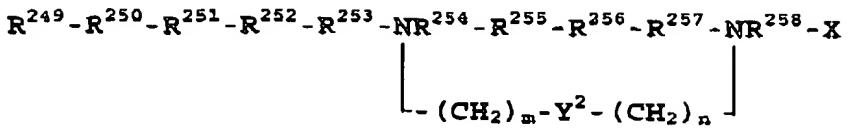
3. The backbone cyclized analog of claim 1 wherein the peptide sequence incorporates at least one D-isomer of an amino acid.

4. The backbone cyclized analog of claim 1 wherein the peptide sequence incorporates at least two D-isomers of an amino acid.

5. The backbone cyclized analog of claim 1 wherein the linear peptide sequence is derived from the IL-6 receptor.

6. The backbone cyclized analog of claim 1 wherein the linear peptide sequence is derived from the IL-6 molecule.

7. The backbone cyclized analog of claim 1 having the general formula 1:



Formula No. 1

wherein m and n are 1 to 5;

X designates a terminal carboxy acid, amide or alcohol group;

R^{249} is Trp, (L) or (D)Lys, (L) or (D) Tyr or (D)Phe;

R^{250} is Arg;

R^{251} is (L) or (D)Leu or Lys;

R^{252} is (L) or (D)Arg;

R^{253} is (D)- or (L)- Phe;

R^{254} is Ala;

R^{255} is (D)- or (L)- Leu or is Lys;

R^{256} is absent or is (L) or (D) Arg;

R^{257} is (L) or (D) Tyr;

R^{258} is Ala; and

Y^2 is amide, thioether, thioester or disulfide.

8. The backbone cyclized analog of claim 7 wherein

R^{249} is Trp, (L)- or (D)- Lys or (D)Phe;

R^{250} is Arg;

R^{251} is Lys or (D)Leu;

R^{252} is (D)Arg;

R^{253} is (D)- or (L)- Phe;

R^{254} is Ala;

R^{255} is (D)- or (L)- Leu;

R^{256} is absent or is Arg;

R^{257} is (D)Tyr;

R^{258} is Ala; and

Y^2 is amide, thioether, thioester or disulfide.

9. The backbone cyclized IL-6 antagonist of claim 8 having the formula:

Trp-Arg-Lys-(D)Arg-Phe-AlaC3-Leu-Arg-(D)Tyr-AlaN3-NH_2

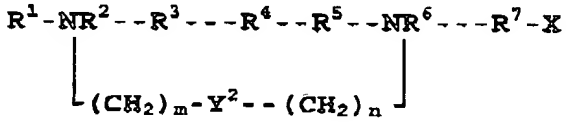
10. The backbone cyclized IL-6 antagonist of claim 8 having the formula: (D)Lys-Arg-(D)Leu-(D)Arg-(D)Phe-AlaC3-(D)Leu-Arg-(D)Tyr-

AlaN3- NH_2

11. The backbone cyclized IL-6 antagonist of claim 8 having the formula:

(D)Phe-Arg-(D)Leu-(D)Arg-(D)Phe-AlaC3-Leu-(D)Tyr-AlaN3-NH_2

29. (New) The backbone cyclized analog of claim 1 having the general formula:



wherein m and n are 1 to 5;

X designates a terminal carboxy acid, amide or alcohol group;

R1 is (D)Bip, Gln, Lys, Lys(ZCL) Dab or absent;

R2 is (L) or (D)Lys, Gly, Ala, (D)Phe or Trp;

R3 is (D) Cit, Lys, (D)Bip or absent;

R4 is Orn, 4PyrAla, (L) or (D)Dab, (L) or (D)Arg, Lys or Dpr;

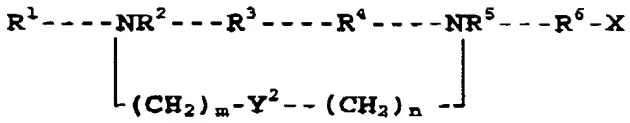
R5 is HomArg, Orn, Lys, Lys(ZCL), Arg, Arg(Mtr) or (D)Glu;

R6 is Asn, (L) or (D)Trp, (D)Gln or (D)Ala;

R7 is Arg, (L) or (D)Trp, (L) or (D)Gln, Abu, Glu or (p-NO2)Phe; and

Y2 is amide, thioether, thioester or disulfide.

30. (New) The backbone cyclized analog of claim 29 having the general formula 3:



Formula No. 3

wherein m and n are 1 to 5;

X designates a terminal carboxy acid, amide or alcohol group;

R^1 is (D)Bip, Gln, Lys, Lys(ZCL) or Dab;

R^2 is (D)Lys, Gly, Ala or Trp

R^3 is Orn, 4PyrAla, (L) or (D)Dab, (D)Arg , Lys or Dpr;

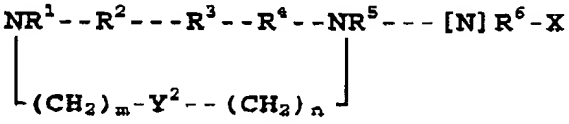
R^4 is Lys, Lys(ZCL), Arg, Arg(Mtr) or (D)Glu;

R^5 is Asn, Trp or (D)Ala;

R^6 is Arg, (p-NO_2)Phe, (L) or (D)Trp, Gln, Abu or Glu; and

Y^2 is amide, thioether, thioester or disulfide.

31. (New) The backbone cyclized analog of claim 29 having the general formula 4:



Formula No. 4

wherein m and n are 1 to 5;

X designates a terminal carboxy acid, amide or alcohol group;

R^1 is (D)Phe or Lys;

R^2 is (D)Cit, Lys or (D)Bip;

R^3 is Dpr, 4PyrAla or (L) or (D)Arg;

R^4 is HomArg, Orn or Lys;

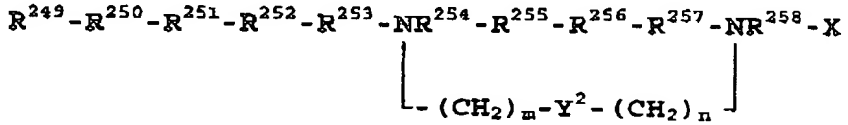
R^5 is (D)Gln or (L) or (D) Trp;

R^6 is (L) or (D)Gln or (p-NO_2)Phe; and

Y^2 is amide, thioether, thioester or disulfide.

32. (New) A pharmaceutical composition comprising a backbone cyclized IL-6 antagonist comprising a peptide sequence of five to twenty amino acids that incorporates at least one building unit, said building unit containing one nitrogen atom of the peptide backbone connected to a bridging group comprising an amide, thioether, thioester or disulfide, wherein the at least one building unit is connected via the bridging group to form a cyclic structure, together with a pharmaceutically acceptable carrier or diluent.

33. (New) The pharmaceutical composition of claim 14 wherein the IL-6 antagonist is a backbone cyclized peptide analog having the general formula 1:



Formula No. 1

wherein m and n are 1 to 5;
X designates a terminal carboxy acid, amide or alcohol group;
R^{249} is Trp, (L) or (D)Lys, (L) or (D)Tyr or (D)Phe;
R^{250} is Arg;
R^{251} is (L) or (D)Leu or Lys;
R^{252} is (L) or (D)Arg;
R^{253} is (D) or (L)Phe;
R^{254} is Ala;
R^{255} is (D) or (L)Leu or is Lys;
R^{256} is absent or is (L) or (D)Arg;
R^{257} is (L) or (D)Tyr;
R^{258} is Ala; and
Y^2 is amide, thioether, thioester or disulfide.

34. (New) The pharmaceutical composition of claim 33 wherein

the IL-6 antagonist is a backbone cyclized peptide analog having the formula:

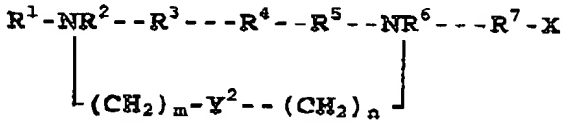
Trp-Arg-Lys-(D)Arg-Phe-AlaC3-Leu-Arg-(D)Tyr-AlaN3-NH_2

35. (New) The pharmaceutical composition of claim 33 wherein the IL-6 antagonist is a backbone cyclized peptide analog having the formula: (D)Lys-Arg-(D)Leu-(D)Arg-(D)Phe-AlaC3-(D)Leu-Arg-(D)Tyr-AlaN3-NH_2

36. (New) The pharmaceutical composition of claim 33 wherein the IL-6 antagonist is a backbone cyclized peptide analog having the formula:

(D)Phe-Arg-(D)Leu-(D)Arg-(D)Phe-AlaC3-Leu-(D)Tyr-AlaN3-NH_2

37. (New) The pharmaceutical composition of claim 32 wherein the IL-6 antagonist is a backbone cyclized peptide analog having the general formula:



wherein m and n are 1 to 5;

X designates a terminal carboxy acid, amide or alcohol group;

R1 is (D)Bip, Gln, Lys, Lys(ZCL) Dab or absent;

R2 is (L) or (D)Lys, Gly, Ala, (D)Phe or Trp;

R3 is (D) Cit, Lys, (D)Bip or absent;

R4 is Orn, 4PyrAla, (L) or (D)Dab, (L) or (D)Arg, Lys or Dpr;

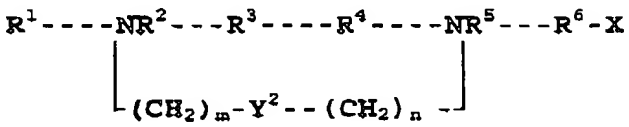
R5 is HomArg, Orn, Lys, Lys(ZCL), Arg, Arg(Mtr) or (D)Glu;

R6 is Asn, (L) or (D)Trp, (D)Gln or (D)Ala;

R7 is Arg, (L) or (D)Trp, (L) or (D)Gln, Abu, Glu or (p-NO2)Phe; and

Y2 is amide, thioether, thioester or disulfide.

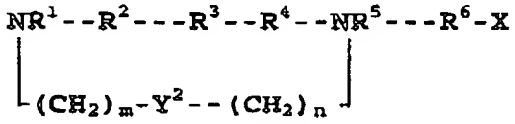
38. (New) The pharmaceutical composition of claim 37 wherein the IL-6 antagonist is a backbone cyclized peptide analog having the general formula 3:



Formula No. 3

wherein m and n are 1 to 5;
X designates a terminal carboxy acid, amide or alcohol group;
R^1 is (D)Bip, Gln, Lys, Lys(ZCL) or Dab;
R^2 is (D)Lys, Gly, Ala or Trp
R^3 is Orn, 4PyrAla, (L) or (D)Dab, (D)Arg , Lys or Dpr;
R^4 is Lys, Lys(ZCL), Arg, Arg(Mtr) or (D)Glu;
R^5 is Asn, Trp or (D)Ala;
R^6 is Arg, (p-NO2)Phe, (L) or (D)Trp, Gln, Abu or Glu; and
Y^2 is amide, thioether, thioester or disulfide.

39. (New) The pharmaceutical composition of claim 37 wherein the IL-6 antagonist is a backbone cyclized peptide analog having the general formula 4:



Formula No. 4

wherein m and n are 1 to 5;
X designates a terminal carboxy acid, amide or alcohol group;
R^1 is (D)Phe or Lys;
R^2 is (D)Cit, Lys or (D)Bip;
R^3 is Dpr, 4PyrAla or (L) or(D)Arg;

R^4 is HomArg, Orn or Lys;

R^5 is (D)Gln or (L) or (D)Trp;

R^6 is (L) or (D)Gln or (p-NO_2)Phe; and

Y^2 is amide, thioether, thioester or disulfide.